REMARKS

Claims 1 to 3 and 10 to 14 were examined in this Office Action. Upon entry of the amendments, claims 1 to 11, 15 to 40, and 55 to 65 will be pending. Claims 4 to 9 and 15 to 40 have been withdrawn by the Examiner. Applicants propose to cancel claims 12 to 14 and 41 to 54 without prejudice. Applicants propose to amend claim 1 to recite "systemic tissue damage" and claim 2 to recite "vasoactive agent therapy." Applicants also propose to add new claims 55 to 65 which recite, *inter alia*, specific dosage regimens and blood transfusions. Support for the amendment to claim 1 can be found throughout the specification, e.g., at claim 12 as originally filed. Support for the new claims can also be found throughout the specification, e.g., at page 8, lines 14-18 and 22-25, page 18, lines 2 to 6, and at original claim 38. The amendments and new claims would add no new matter to the application.

Withdrawn Rejections

Applicants assume that since the rejection of claims 1 to 3 and 10 to 14 as allegedly anticipated by Grinstaff et al. (U.S. Patent No. 5,498,241) has not been restated in the present Office Action, this rejection has been withdrawn.

Rejections under 35 USC §112, Paragraph 1

Claims 1 to 3 and 10 to 14 remain rejected as allegedly not enabled. For reasons unrelated to the present rejection, applicants propose to cancel claims 12 to 14 without prejudice, thereby obviating the rejection with respect to those claims. However, applicants again traverse this rejection with respect to claims 1 to 3, 10 and 11. Further, applicants point out that they have added new claims 55 and 56, which recite dosage regimens, and new claims 57 to 65, which recite blood transfusions.

In the Office Action at page 5 under the section entitled "Response to Arguments," the Office lists as Items (A) through (I) the Office's characterizations of applicants' arguments

against the rejection and attempts to address each one in turn. For the sake of clarity, applicants will in this Reply maintain the Office's lettering scheme (but not necessarily the same order).[1]

Item A – Interview Summary Regarding Related Applications

In applicants' previous Reply, applicants attached (as Appendix 1) an Interview Summary they received in U.S. Serial No. 10/439,632. Versions of this Interview Summary were received by applicants in related U.S. Serial Nos.10/177,930, 10/053,535, 10/367,277, 10/371,666, 10/413,817, 10/439,632, 10/455,564, and 10/600,182. Applicants also attached (as Appendix 2) a Reply they filed in U.S. Serial No. 10/439,632, which addressed the enablement issues raised in the Interview Summary. In doing so, it was not applicants' intention to encourage the Office to engage in speculation about what was discussed during the interview. Rather, applicants brought the Interview Summary to the Examiner's attention because the enablement issues addressed in the related applications may be relevant to this application. As the Office has reproduced text from the Interview Summary in the present Office Action and applicants in their Appendix 2 thoroughly addressed the issues raised there, applicants assume that the Office is now fully aware of these issues and has considered them in the context of the present claims.

Item B – References Cited in the Interview Summary

The Office Action states in this item that:

> The references applicant wants this examiner to disclaim, that is, Mayr, Ryter, Dolinay and Choi are not of record in this application 10/676,280 and making judgments and according relevance or irrelevance on those references at this time would be premature in the examination of this application since each statement or record proceeds independently based on the facts presented in that case at any stage in the examination process.

Applicants respectfully disagree. Each of these references was cited in an Information Disclosure Statement (IDS) filed on August 23, 2006. Their entries were initialed as considered

[1] Applicants do not agree that the Office's *characterizations* of the arguments are correct. Applicants' arguments are clear, of record, and stand on their own. In the interest of maintaining a clear record and efficiency, applicants have addressed here only the Office's *responses* to the arguments and not the Office's characterizations of them.

by the Examiner in an initialed copy dated December 31, 2006. A copy of the initialed IDS is available on PAIR, and is also attached hereto for the Examiner's convenience as Appendix A. Thus, Mayr, Ryter, Dolinay and Choi are indeed of record in this application, and were presumably thoroughly reviewed by the Examiner in 2006. Applicants therefore respectfully assert that it is not at all premature to make judgments and accord relevance or irrelevance to these references at this time. Applicants again request that the Examiner acknowledge for the record that in view of the evidence and arguments provided in their previous Reply, the scope of enablement issues raised in the Interview Summary will not be applied against the present claims.

Items C and D – Omaye et al. and Issues of Toxicity and Side Effects

The Office in this item appears to acknowledge that issues of toxicity and side effects are irrelevant to the Office's proper determination of whether applicants' claims comply with United States patent law (here, the enablement requirement). Nevertheless, the Office states that the "outstanding issue is the scope of the enabling disclosure relative to the scope of the claims." The Office Action recites the Office's guidelines for examining claims for compliance with the enablement requirement and concludes (at page 8):

> Now, claim 1 is seeking protection for all and every amount of CO to be administered to a subject having hemorrhagic shock. The specification envisions specific concentrations for treating hemorrhagic shock. The protection sought by the claim is broader than what is enabled by the disclosure. The Omaye reference is a negative teaching and raises the issue of what levels of CO is enabled. The PTO does not have laboratories.

In their previous Reply, applicants argued, *inter alia*, that the fact that CO is potentially toxic, as is simply confirmed by Omaye's description of untoward side effects a patient might experience when exposed to various levels of CO, does not justify the Office's requirement that applicants limit their claims to administering specific dosages of CO. Applicants believe that those arguments completely address this issue and incorporate them herein by reference.

As applicants understand it, the Office nevertheless remains unconvinced because it somehow views Omaye's teachings as proof that a practitioner could not practice applicants' methods unless dosage levels were explicitly recited in the claims. The Office's logic appears to

be that because Omaye contains a description of side effects that can occur in a patient exposed to, e.g., an ambient concentration of 70 ppm, and because applicants' claims, which do not recite a specific dosage level, encompass administering 70 ppm, a skilled practitioner would be rendered helpless to perform the methods using such dosage levels and would have to resort to undue experimentation to figure out how to make the method work. Thus, according to the Office, the full scope of the claims is not enabled.

Applicants respectfully submit that this reasoning is deeply flawed. This becomes evident upon a full consideration of the arguments and information applicants provided in their previous Reply. As applicants pointed out there, the specification provides a large amount of information that teaches skilled practitioners how to administer CO to patients. The specification also provides an *in vivo* working example wherein applicants proved that 250 ppm was effective in a mouse model of hemorrhagic shock. At the time the present application was filed, the literature was rich with information regarding, e.g., what levels of CO exposure can produce what sorts of toxicity in humans and animals, ways to monitor and counter the toxic effects of CO, and methods of determining CO levels in patients, estimating CO uptake, and administering CO to patients for testing pulmonary function.

Practitioners who wished to treat hemorrhagic shock using dosage levels (e.g., 70 ppm) other than that used in applicants' *in vivo* example and/or in other animals needed only to refer to the specification and the art and, if necessary, perform what would be considered routine and reasonable experimentation in the arts of drug development and medicine in order to do so. For example, adjusting the amount of time a patient is exposed to a particularly high or low dose of CO to achieve the desired result and/or avoid unacceptable levels of toxicity was clearly within the skill set of those of ordinary skill in the art. Thus, the broad scope of the present claims is completely justified and the claims are fully enabled.

Despite all of the evidence militating in favor of enablement of the full scope of the pending claims, the Office Action (at page 8) refers to Omaye as "negative teaching" that "raises the issue of what levels of CO is [sic] enabled." However, the fact that Omaye reports various side effects does not somehow "negate" the detailed teachings of the specification, the enormous amount of information in the art, and the high level of skill of practitioners in the art. Any experimentation that may be required to perform the claimed methods using any particular

dosage level would have been routine and cannot in any way fairly be considered "undue." The Office has presented no evidence suggesting otherwise.

Items E, F and I - Limitations Not Present in the Claims and the Office's Assertion that Applicants' Arguments Support the Office's Position

The Office under these three Items asserts that applicants' own arguments have somehow supported the Offices' position, stating (at page 9, under both Items E and F):

> Applicant's reference to certain amounts of CO in the specification supports the finding that the scope of enablement provided to one of skill in the art by the disclosure is not commensurate with the scope of protection sought by the claims. By arguing for limitations that are not in the claims but in the specification, applicant is attempting to import limitations from the specification into the claims.

For the record, applicants respectfully state here that none of the arguments provided in the previous Reply supports the Office's rejection. Applicants have not in any way attempted to import limitations into the claims. Rather, as discussed above, applicants in the previous Reply explained to the Office that, although the examined claims quite properly do not recite dosage limitations, skilled practitioners were fully enabled to perform the full scope of the claimed methods, including at whatever dosages were needed. In explaining this in the previous Reply, applicants referred to, *inter alia*, the specification, the working example, the art, and Exhibit D[2], all of which of course mention certain dosages of CO. Applicants' mention of these dosage levels in the broader context of applicants' arguments for enablement of the full scope of the claims does not somehow prove that dosage limitations should be recited in the claims or amount to an attempt by applicants to import limitations into the claims.

Items G and H - Applicants' Discussion of Nitric Oxide

In their previous Reply, applicants referred at several points to the well-known medical uses of nitric oxide (NO). In the Office Action under these two Items, the Office appears to have

[2] Exhibit D was an attachment to applicants' previous Reply that provided for the Office's consideration a clinical protocol published after the present application's filing date. The protocol described a method of delivering CO that is encompassed by the teachings of applicants' specification.

taken issue with and/or dismissed applicants' point about NO, stating (at page 10 under Items G and H):

> The invention is not to the administration of NO to save lives and it would appear that NO is administered at specified levels/concentrations.
>
> Regarding H), the claimed invention is not directed to the use of NO and the PTO is not the FDA.

Applicants respectfully submit that the Office seems to have misinterpreted applicants' points about NO. Applicants discussed NO in their previous Reply for several reasons. First, as explicitly stated at page 12 of the previous Reply, applicants believe it is evidence that skilled practitioners understood that toxic gases could be useful therapeutics when properly handled. Accordingly, applicants discussed the inhaled NO field during their review of the Wands factors under the section entitled "The State of the Prior Art." Second, applicants believe that the state of the inhaled NO art at the time the present application was filed is indicative of the high level of skill of health care professionals in administering potentially toxic gases to patients. Accordingly, applicants discussed the inhaled NO field during their review of the Wands factors under the section entitled "the Relative Skill of Those in the Art." Applicants assert that these were valid points in their argument for enablement of the presently claimed methods and that these have not reasonably been addressed in the present Office Action.

For the reasons stated above, applicants maintain that a thorough examination of the specification and a rigorous application of the *Wands* factors would lead the Office to the conclusion that the present claims are in full compliance with the enablement requirement. Skilled practitioners would clearly have been able to practice the full scope of the invention recited in the claims, especially when armed with applicants' specification and the knowledge of those of ordinary skill in the art. Accordingly, applicants request withdrawal of the rejection for lack of enablement. Applicants also request that the rejection not be applied to new claims 55 and 56, which recite dosage regimens, and new claims 57 to 65, which recite blood transfusions.

Rejections Under 35 U.S.C. §102

Claims 1 to 3 and 10 to 14 remain rejected as allegedly anticipated by Fujita et al., Nat. Med. 7: 598-604 (2001) (hereinafter "Fujita"). Claims 1 to 3 and 10 to 14 also remain rejected as allegedly anticipated by Pinsky et al. (US Publication No. 2005/0048133). The Office again cites Bar-Or (U.S. Publication No. 2005/0215468) (hereinafter "Bar-Or") to support the Office's proposition that Fujita's (and in this Office Action, Pinsky's) recitation of "ischemia" is equivalent to a recitation of "hemorrhagic shock." For reasons unrelated to the present rejection, applicants propose to cancel claims 12 to 14 without prejudice, thereby obviating the rejection with respect to those claims. However, applicants again traverse this rejection with respect to claims 1 to 3, 10 and 11. In this Reply, applicants will first address the Office's construction of "ischemia" in view of Bar-Or and then turn to a discussion of Fujita and Pinsky.

The present and previous Office Actions both state that Bar-Or "describes ischemia as hemorrhagic shock in a more generalized sense." In their previous Reply, applicants explained in detail why Bar-Or does not support the Office's changing of the commonly understood definition of "ischemia" to include or be synonymous with "hemorrhagic shock." The Office has apparently dismissed those arguments. Thus, in response to applicants' arguments against anticipation by Fujita, the Office stated (at page 12) "[c]laim 1 treats hemorrhagic shock in a patient and Bar-Or is a prior art that describes ischemia as hemorrhagic shock and applicant's argument does not negate the teaching of Bar-Or." Likewise, with respect to applicants' arguments that the claims are not anticipated by Pinsky, the Office stated "[w]hile Pinksy does not specifically state hemorrhagic shock, applicant admits that Pinsky is involved with ischemia and ischemia as per the teaching of Bar-Or is hemorrhagic shock."

Applicants respectfully submit that the Office has not addressed applicants' points about Bar-Or (and Fujita and Pinsky, which will be addressed below). Applicants sought not to *negate* the teachings of Bar-Or, but rather to show that the Office Action was incorrect about what Bar-Or teaches. Applicants understand the Office to be referring to Bar-Or's statement at [0004] that "[i]schemia need not be limited to one organ; it can also be more generalized (e.g., in hemorrhagic shock)." Applicants have neither disputed nor, contrary to what is asserted in the Office Action, attempted to "negate" this statement. Generalized ischemic injury can indeed occur in hemorrhagic shock. But the statement cannot fairly be used by the Office as a license to

construe the terms "ischemia" and "hemorrhagic shock" as one and the same, i.e., as interchangeable terms. Such a construction would render Bar-Or's own teachings nonsensical. Consider Bar-Or's discussion (at [0004]) of certain types of ischemias, such as "cardiovascular ischemia," "cerebral ischemia," and ischemia that occurs in individual organs such as "kidney, liver, lung, and the intestinal tract." Bar-Or's categorization of these types of ischemia would seem to have no meaning if all were construed to mean "hemorrhagic shock." There mere fact that one potential outcome of hemorrhagic shock can be generalized ischemia does not mean that hemorrhagic shock and ischemia are the same thing. Ischemia can certainly occur in the absence of hemorrhagic shock. Applicants therefore submit that "ischemia" and "hemorrhagic shock" cannot properly and fairly be construed by the Office as interchangeable terms.

Turning now to Fujita and Pinsky, applicants assert that neither reference can properly be found to anticipate claims 1 to 3 and 10 to 14. These claims are limited to treatment of hemorrhagic shock. Fujita demonstrated that CO improved survival of mice who had been subjected to experimentally induced lung ischemia. Fujita does not state, or even suggest, that the mice experienced hemorrhagic shock or any type of generalized ischemia. The ischemia surgically induced in the mice was attributable to clamping of a blood vessel to temporarily prevent blood flow in a localized area of a lung, and not due to bleeding (i.e., hemorrhage) at all (see the Methods section of Fujita). There is simply no evidence that Fujita's mice experienced any blood loss at all, much less the sort of massive blood loss that can lead to hemorrhagic shock.[3] As discussed above, Bar-Or does not support the Office's position that Fujita's recitation of lung "ischemia" is the same as a recitation of "hemorrhagic shock." Fujita therefore fails to disclose each and every limitation of applicants' methods and does not anticipate the pending claims

Likewise, Pinsky fails to anticipate claims 1 to 3 and 10 to 14. Pinsky says at [0059] that:

> "[I]schemic disorder" encompasses and is not limited to a peripheral vascular disorder, a venous thrombosis, a pulmonary embolus, a myocardial infarction, a transient ischemic attack, lung ischemia, unstable angina, a reversible ischemic neurological deficit, adjunct thromolytic (sic) activity, excessive clotting conditions, sickle cell anemia or a stroke disorder.

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[3] See the discussion of hemorrhagic shock in the specification at page 1, lines 16-19.

Each of the conditions listed in the quoted text appears to involve ischemia at a discrete site. Nowhere does Pinsky even mention the term "hemorrhagic shock" or anything equivalent thereto, much less teach, or even suggest, that CO could be used to treat this disorder. It is clear from all of the references of record that "ischemia" can occur in many different sorts of conditions that have nothing to do with the massive blood loss that can lead to hemorrhagic shock. Because Pinsky fails to teach or suggest all elements of applicants' methods, it does not anticipate the pending claims.

Applicants therefore request that the rejections of the claims as allegedly anticipated by Fujita and Pinsky be reconsidered and withdrawn. Applicants also request that the rejection not be applied to new claims 55 to 65.

CONCLUSION

Applicants submit that all pending claims are in condition for allowance, which action is requested. Enclosed is a Petition for Three Month Extension of Time. Please apply the charge of $1050 for the required fee to Deposit Account No. 06-1050. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 14022-011001.

Respectfully submitted,

Date: April 4, 2008

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Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 14022-011001	Application No. 10/676,280
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR 1.98(b))		Applicant Billiar et al.	
		Filing Date September 30, 2003	Group Art Unit Unknown

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	A1						
	A2						
	A3						

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No
	B1							
	B2							
	B1							
	B2							
	B3							

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
BF	C1	Choi et al., "'Therapeutic' carbon monoxide may be a reality soon," Am. J. Respir. Crit. Care Med., 171(11):1318-1319 (2005)
BF	C2	Dolinay et al., "Can Inhalation Carbon Monoxide be utilized as a therapeutic modality in human diseases?", pp. 203-236 in *Breath Analysis for Clinical Diagnosis and Therapeutic Monitoring*, Amann and Smith, eds., World Scientific Publishing Company (2004)
BF	C3	Dolinay et al., "Inhaled carbon monoxide confers antiinflammatory effects against ventilator-induced lung injury," Am. J. Respir. Crit. Care Med. 170:613-20 (2004)
BF	C4	Mayr et al., "Effects of carbon monoxide inhalation during experimental endotoxemia in humans," Am. J. Respir. Crit. Care Med., 171:354-360 (2005)
BF	C5	Ryter et al., "Therapeutic applications of carbon monoxide in lung disease," Curr. Opin. Pharmacol., 6:257-262 (2006)
BF	C6	Ryter et al., "Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications," Physiol. Rev. 86(2):583-650 (2006)
BF	C7	Thom et al, "'Therapeutic' Carbon Monoxide May Be Toxic," Am. J. Respir. Crit. Care Med., 171(11):1318 (2005)
	C8	

Examiner Signature	Date Considered
/Blessing Fubara/	12/31/2006

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.